REMARKS

Claims 1-7 are presently pending. Claims 1 and 5 have been amended. Claims 8-77 have been previously withdrawn for prosecution at a later date.

The outstanding issues in the outstanding office action are addressed individually below.

1. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-7 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention (see Office Action, pg. 3). More specifically, the term "greater than" was said allegedly to render claims 1-7 indefinite (see Office Action, pg. 3). Applicants respectfully traverse this rejection.

According to MPEP § 2171 and § 2173, the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant so as to inform the public of the boundaries of what constitutes infringement of the patent. Under this rationale, acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification (see MPEP § 2173.05(b)). Accordingly, an Examiner must review the claim in its entirety to determine whether the claim at issue apprises one of ordinary skill in the art of its scope, and therefore serves the notice function required by § 112, second paragraph.

Under this analytical framework, the primary inquiry under §112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language is available (see MPEP § 2173.02). Relative terminology in a claim does not render the claim automatically indefinite under § 112, ¶2 (see MPEP § 2173.05(b)). In addition, imprecision of claim terminology does not render a claim indefinite so long as one of ordinary skill in the art would understand the scope of the claimed invention (see MPEP § 2173.05(b)).

Applicants respectfully aver that the use of the term "greater than" does not render claims 1-7 indefinite. The term "greater than" has a common usage, which means "comparatively larger in dimension; more considerable in degree, intensity, quantity; or larger in number" (see

Webster's Dictionary, 3rd Ed., Random House, Ballantine Books, New york, 1998). In the context of the claims, one of skill in the art of cancer research and therapy would recognize that the level of triosephosphate isomerase expression on a test neoplastic cell must be detectably "greater than" the level of triosephosphate isomerase expression identified on a control, nonresistant, neoplastic cell. The control, nonresistant, neoplastic cell is a control cancer cell that has detectably less cell surface expression of triosephosphate isomerase protein than multidrug resistant cancer cells (see Specification, pg. 20, ll. 19-26). A control, nonresistant, neoplastic cell merely provides a detectable level of cell surface-expressed triosephosphate isomerase for comparison against the level of cell surface-expressed triosephosphate isomerase detected on the test neoplastic cell (see id.). The exact "degree" of increased cell surface triosephosphate isomerase expression on the test cell as compared to the control nonresistant, neoplastic cell is not important as any amount of triosephosphate isomerase that can be detected on the cell surface of the test neoplastic cell greater than the amount of triosephosphate isomerase detected on the cell surface of the control, nonresistant, neoplastic cell is indicative of multi-drug resistance.

Solely to the facilitate prosecution Applicants, have amended claim 1 to recite that "the level of cell surface-expressed triosephosphate isomerase in the test neoplastic cell is detectably greater than the level of cell surface-expressed triosephosphate isomerase..." Support for this amendment can be found in the specification, *inter alia*, at page 26, lines 25-30 and page 30, lines 5-22. Modes of detecting triosephosphate isomerase on the surface of the test and control neoplastic cells are described in the specification at page 26, lines 25-30 and page 30, lines 5-22.

In view of this Amendment and argument, Applicants respectfully request that the rejection of claim 1 be reconsidered and withdrawn.

Likewise, the rejection of claims 2-7, which depend from claim 1 and thus contain all the limitations thereof, should also be reconsidered and withdrawn.

2. *Rejections Under 35 U.S.C. § 112, First Paragraph*

Claims 1-7 also were rejected under 35 U.S.C. § 112, first paragraph, for not being enabled. The Office Action opined that "undue experimentation" is required to practice the claimed invention because the specification does not provide sufficient disclosure to establish that cell surface-expression of triosephosphate isomerase on multidrug-resistant cell lines correlates with multidrug resistance in tumors *in vivo* (see the Office Action, pp. 3-7). The Office Action based its allegations of lack of enablement on prior art references that allegedly establish that there is no correlation between the results identified *in vitro* and the cell characteristics or behavior found *in vivo*. Applicants respectfully traverse this rejection.

According to MPEP § 2164.05(b), the specification must be enabling to those of skill in the relevant art to which the claimed invention pertains at the time the application was filed. A disclosure can be enabling, while requiring experimentation to perform the claimed invention, provided that the experimentation required is not "undue." The quantity of experimentation needed to be performed by one of skill in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention (see MPEP § 2164.06). However, the test is not "merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (see MPEP § 2164.06). In the chemical arts, time and difficulty of experiments are not determinative if they are merely routine (see MPEP § 2164.06).

Enablement of a claimed invention requires a correlation between the *in vivo* or *in vitro* model used in the application and the disclosed method of use (MPEP § 2164.02). The issue of correlation is dependent on the state of the art. If the prior art shows that a correlation exists between a particular model and a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate (MPEP § 2164.02). It should be noted that a rigorous or invariably exact correlation is not required where the disclosure of pharmacological activity is reasonable based upon the probative evidence (MPEP § 2164.02, quoting *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed.Cir. 1985)).

Applicants respectfully assert that a correlation exists between established cancer cell lines and primary tumors. Those of skill in the art have long relied upon cell lines to provide reliable and predictable data on cancer and multidrug resistance as cell lines mimic *in vivo* cancer phenotypes (see, *e.g.*, Gao *et al.* (2000) *Mol. Pharmacol.* 58(5):1001-10). Such data from cell lines have led to the discovery of important markers of cancer proliferation and drug resistance (see, *e.g.*, Falzon *et al.* (2000) *Endocrinol.* 141(5): 1882-92). Furthermore, the cell lines used in the Examples are well known models for cancer and drug resistance, and are recognized in cancer research as being predictive of the *in vivo* behavior of cancer cells (see, *e.g.*, Falzon *et al.* (2000) *Endocrinol.* 141(5): 1882-92; Gao *et al.* (2000) *Mol. Pharmacol.* 58(5):1001-10; Peterson *et al.* (1991) *Biochem. Biophys. Res. Commun.* 179(1): 661-7). Thus, those of skill in the art have long recognized the useful correlation between cell lines and in tumors.

In light of such a correlation and in view of the specification teachings, Applicants aver that merely routine experimentation would be required to practice the claimed invention. For example, the application provides detailed disclosures on how practice the claimed invention. Specifically, the application discloses how to make and use triosephosphate isomerase-binding agents, which are used to detect to cell surface-expressed triosephosphate isomerase (see specification, pg. 28, l. 26-pg. 30, l.30). Moreover, the application discloses how to obtain control, nonresistant, neoplastic cells and from where to obtain test neoplastic cells (see Example 1, Table 1). The specification also teaches exemplary embodiments of the claimed invention (see specification, pg. 30, l. 21-pg. 32, l. 17). For example, test neoplastic cells and control, nonresistant, neoplastic cells are isolated and fractionated to yield plasma membrane fractions (see specification, pg. 49, ll. 13-19; and pg. 27, ll. 1-4). The level of cell surface-expressed triosephosphate isomerase in the plasma membrane fraction of the test neoplastic cells and control nonresistant, neoplastic cells is detected by FACS analysis, cell surface biotinylation, immunoprecipitation or immunofluorescent analysis (see specification, pg. 26, ll. 26-30). Therefore, the specification provides adequate teachings to allow one of skill in the art to practice the claimed invention with merely routine experimentation.

Accordingly, Applicants respectfully request that this § 112, first paragraph, rejection be reconsidered and withdrawn.

Likewise, claims 2-7, all of which depend from claim 1 and thus contain all the limitations thereof, do not require "undue experimentation" and are enabled under § 112, first paragraph.

Claims 1-7 were also rejected under 35 U.S.C. § 112, first paragraph, for not being enabled. The rejection was based on the contention that the triosephosphate isomerase marker requires further validation in human populations (see Office Action, pg. 8). The Office Action alleged that the Tockman reference (Tockman *et al.* (1992) *Cancer Res.* 52:2711s-2718s) ("Tockman") teaches that validation is necessary to establish successful application of a marker and to show that the invention will function as claimed (see the Office Action, pp. 8-9). The Office Action opines that Tockman shows that without validation of triosephosphate isomerase as a diagnostic marker of multidrug resistance, one of skill in the art would not be able to predict that the claimed invention works for its intended purpose, and therefore undue experimentation is required to practice the claimed invention (see Office Action, pp. 8-9). Applicants respectfully traverse this rejection.

According to MPEP § 2164, the enablement requirement demands that the specification of an application describe how to make and use a claimed invention. Enablement merely requires that the specification describe the claimed invention to the interested public in a meaningful way (see MPEP § 2164). However, compliance with 35 U.S.C. § 112 does not require that the specification "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect" (see § 2164).

Applicants assert that the Tockman reference does not establish that a marker must be tested against population studies prior to being recognized or established as a diagnostic marker. Those skilled in the cancer research art have identified markers without such testing (see, *e.g.*, Falzon *et al.* (2000) *Endocrinol.* 141(5): 1882-92; Gao *et al.* (2000) *Mol. Pharmacol.* 58(5): 1001-10; Peterson *et al.* (1991) *Biochem. Biophys. Res. Commun.* 179(1): 661-7). Thus, those of skill in the art would understand the Tockman reference teaches the steps required to obtain

regulatory approval, such as FDA approval, for the use of a marker as a cancer detection agent (see Tockman *et al.* (1992) *Cancer Res.* 52: 2716s, Summary).

Those of skill in the art would recognize that the invention works for its intended purpose because the cell lines are well known models for cancer that have been used extensively prior to the filing of the above-referenced application (see, *e.g.,* Falzon *et al.* (2000) *Endocrinol.* 141(5): 1882-92; Gao *et al.* (2000) *Mol. Pharmacol.* 58(5): 1001-10; Peterson *et al.* (1991) *Biochem. Biophys. Res. Commun.* 179(1): 661-7). In addition, cell lines are considered reliable models that produce data that is predictive of cancer and multidrug resistance *in vivo* (see id.). Accordingly, the specification enables the claimed invention without the need for further validation because one of skill in the art would expect that the claimed invention works for its intended purpose.

Accordingly, Applicants respectfully request that the § 112, first paragraph, rejections be reconsidered and withdrawn.

Likewise, claims 2-7, all of which depend from claim 1, and thus contain all the limitations thereof, do not require validation under § 112, first paragraph.

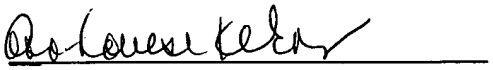
CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully request the rejections contained in the Office Action mailed on August 10, 2006 be reconsidered and withdrawn. Applicants also submit that the pending claims are in condition for allowance.

No fees are due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,



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